REMARKS

Status of the Claims

Claims 1-75 were pending.

Claims 1-35 and 71-75 stand rejected under Sections 112 and 103.

Claims 36-70 were withdrawn from consideration.

Claims 9-12, 24-25, 29-31, 36-70, 73, and 75 are canceled herein, without prejudice.

Claims 1 through 8, 13 through 23, 26 through 28, 32 through 35, 71, 72, and 74 are amended herein.

Claims 76 through 100 are new claims.

Reconsideration is respectfully requested.

Below is a discussion of (1) the election requirement, (2) the amendments to the claims, and (3) the rejections set forth in the Office Action.

I. Election of Species/Restriction Requirement

The Office Action has acknowledged applicants' election of the species, [1S 1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17oxabicyclo[14.1.0]-heptadecane-5,9-dione (Compound 1), and capecitabine for the treatment of cancer.

Applicant has canceled claims 36-70 in view of the restriction requirement and reserves the right to pursue a divisional application with respect to the subject matter thereof.

II. Discussion of Claim Amendments and New Claims

Applicant has amended claims 1 through 8, 13 through 23, 26 through 28, 32 through 35, 71, 72, and 74 herein. New claims 76 through 100 have been added. Besides the cancellation of claims 36-70, discussed above, Claims 9-12, 24-25, 29-31, 73 and 75 have also been canceled. Below is a discussion of these amendments. No new matter has been added.

A. Amendments

Claims 1 through 8, 13 through 23, 26 through 28, 32 through 35, 71, 72, and 74 have been amended for the sake of enhancing the clarity of the claims.

In particular, the claims have been amended to replace the phrase "Formula I compound" with the phrase "the compound of formula I," in response to antecedent basis rejections raised in the Office Action. Similarly, these claims have been amended so that the capitalization of "Claim" and "formula" is consistent throughout the claims, in response to requests in the Office Action for greater consistency.

Claim 1 has further been amended to replace the phrase "proliferative diseases including cancer" with the phrase "cancer" in response to the comment in the Office Action that this phrase recites a preference. Applicant reserves the right to pursue in a divisional or continuation application claims to methods of treating proliferative diseases other than cancer.

Claim 1 and each of the remaining claims herein have been further amended to replace the generic term "anti-proliferative agent" with the term "anti-neoplastic cytotoxic agent" in order to enhance the clarity of the claim scope. The specification herein distinguishes between cytotoxic and cytostatic agents – a distinction that is well known in the field of oncology pharmaceutical products. For example, cytotoxic agents are discussed in the specification herein at (among other points), page 21, line 30, through page 23, line 27, and cytostatic agents are discussed at page 23, line 28, through page 25, line 9. As discussed therein, cytotoxic agents include anti-metabolites such as capecitabine and alkylating agents such as Carboplatin and Cisplatin. Cytostatic agents include, *inter alia*, antiangiogenic and antivascular agents and signal transduction inhibitors such as PDGF inhibitors. Applicant reserves the right to pursue in a divisional or continuation application claims to combinations involving use of cytostatic agents such as signal transduction inhibitors.

Claim 1 has further been amended with respect to the variables Y and B_1, R_1 and R_2, and R_3 and R_4, to improve the grammar and enhance the clarity of the subject matter recited in the claim. It is believed these changes should be self-evident.

Claim 7 has been amended to delete reference to the term "inhibitors of cell cycle progression" as these agents are cytostatic agents such as CDK inhibitors.

Claims 13 and 14 have been further amended to replace the reference to "Compound 5" with the specific name for this compound, which is recited at page 47 of the specification. Similarly, claims 17 through 19 and 33 through 35 have been amended to replace the reference to "Compound 1" with the specific name for this compound, which is found at page 46 of the specification.

Claim 23 has been further amended to recite that the pharmaceutical composition comprises a synergistically effective amount of the cytotoxic agent and compound of formula I. As discussed at various pages of the specification (e.g., pages 2, 9, 26, 55, 56, 68 etc.), applicant has surprisingly discovered that certain epothilone analogs in combination with anti-proliferative agents, including cytotoxic agents such as capecitabine and alkylating agents such as cisplatin, have a synergistic effect in the treatment of cancer. Claim 1 calls for a method involving a synergistic combination and thus, Claim 23 has been amended to consistently recite the invention.

Besides the above, each of the claims reciting a Markush group has been amended to include language to the effect of "and/or mixtures thereof," or "at least one of." These amendments are made in response to the recent decision by the Federal Circuit in *Abbott Labs v. Baxter Pharmaceutical Products, Inc.*, 334 F.3d 1274, 67 USPQ2d 1191 (Fed. Cir. 2003). In *Abbott Labs*, the court held that Markush language "selected from the group consisting of A, B, C, D," can limit the claim to use of *only one of* A, B, C or D, unless qualifying language, *e.g.*, "and mixtures thereof," or "at least one of" is used. Applicant's intent had been to include mixtures within the scope of the Markush grouping. Thus, the claims are amended in response to this case to recite the invention consistently with applicant's intention.

B. Cancellation of Claims

Claims 9 through 12 and 29 through 30 have been canceled as Compounds 2 and 3 (the ras FT inhibitor and CDK inhibitor) are cytostatic agents, not cytotoxic agents as now delineated in the claims. Applicants reserve the right to pursue in a divisional or

continuation application claims to combinations involving use of ras FT inhibitors and CDK inhibitors and other cytostatic agents.

Claims 24 and 25 were canceled as these claims recited an intended use of the composition of Claim 23 and as such, did not further limit the scope of Claim 23.

Claim 31 has been canceled as Compound 5 is Cisplatin and thus, claim 31 was redundant of claim 32.

Claim 73 is canceled because this claim had recited the embodiment where the anti-proliferative agent is a cytotoxic (as opposed to a cytostatic agent). Since each of the claims herein now recite use of a cytotoxic agent, claim 73 was rendered redundant and has thus been canceled.

Claim 75 is canceled because this claim depending on claim 25, a canceled claim.

C. New Claims

Applicant has added new claims 76 through 100 for the purpose of presenting claims directed to the elected species and/or claim the elected invention in alternate ways. For example, new Claims 76 through 79 recite the particular combination of Compound 1 and capecitabine wherein these claims depend upon claims 3, 4, 5 and 6, respectively. New Claims 80, 82, 86 and 98 recite embodiments wherein the additional cytotoxic agent is an anti-metabolite, and claims 81, 83, 87, 89 and 91 recite a Markush grouping of anti-metabolites. The specification at page 8, lines 26 through 31, and page 22, lines 4 through 9, provides support for the claim to anti-metabolites and more particularly, to this grouping of anti-metabolites. Capecitabine is identified at page 20 as an anti-proliferative cytotoxic agent and is a well-known anti-metabolite, i.e., Capecitabine is a prodrug to 5-fluorouracil (5-FU) and is enzymatically converted to 5-FU *in vivo*. 5-FU is identified throughout the specification as an anti-metabolite. *See also* specification at pages 40 and 42 for discussion of 5-FU compounds.

New Claims 84 and 85 are presented to recite a subgenus of compounds of formula I that can be used according to the inventive combination. Support for this subgenus can be found throughout the specification in terms of preferred embodiments, e.g., at pages 26 through 35, and also in original claims 20, 21 and 22.

New claims 88 through 91 are presented to more particularly recite types of cancers that may be treated with the inventive methods. These claims are supported at page 26, lines 1 through 5.

New claims 92 and 93 recite embodiments where the additional cytotoxic agent is an alkylating agent. (*See* spec at p. 21, line 32 and page 56).

Lastly, new claims 94 through 100 (i.e., independent claim 92) are presented to alternatively recite the inventive combination in terms of a pharmaceutical product. Claims 26 through 35 recite the inventive combination in terms of a pharmaceutical composition. However, as discussed at pages 38 and 44 of the specification, the compound of formula I and the anti-neoplastic agent may be administered separately. At page 44, it is particularly recited that the compounds of formula I and the anti-neoplastic agent "do not have to be administered in the same pharmaceutical composition and may, because of different physical and chemical characteristics, have to be administered by different routes." (Page 44, lines 11-15). Thus, the specification supports a product involving separate packages for the compound of formula I and the anti-neoplastic agent, as recited in these new claims.

III. Response to Office Action Rejections

Claims 1-35 and 71-75 stand rejected on grounds of (A) lack of enablement under Section 112, first paragraph; (B) indefiniteness under Section 112, second paragraph; and (C) obviousness under 35 USC § 103(a). Each of these arguments is addressed separately below.

A. Section 112, First Paragraph- Enablement

It appears the lack of enablement rejection is based on the reasoning that the particular types of proliferative diseases to be treated are not recited in the claims. The Office Action acknowledges that the claims are enabling for paclitaxel-resistant cancerous solid and refractory tumors (Office Action at page 3). However, the Office Action then states that the specification is not enabling for the treatment of any and all proliferative diseases in general, or for any and all solid or refractory tumors (OA at p. 4). In support of this argument, the Office Action cites *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and

argues that (1) there is a high level of unpredictability in this field, (2) the claims are broad and inclusive of any and all proliferative diseases, (3) there is little guidance in the specification for types of proliferative diseases other than paclitaxel resistant tumors, and (4) undue experimentation would be required to practice the invention.

Initially, Applicant notes that in response to the Section 112, second paragraph rejection (discussed below), applicant has amended claim 1 to recite a method directed to the treatment of cancer as opposed to the treatment of any and all proliferative diseases. Applicant has reserved the right to pursue claims to methods of treating other proliferative diseases besides cancer in a divisional or continuation application. Applicant believes that this amendment should render the lack of enablement rejection substantially moot. Nonetheless, applicant adds the following, further comments.

When rejecting a claim for lack of enablement, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). This reasonable explanation must involve more than conclusory statements. Rather, the Examiner is required to provide evidence or technical reasoning substantiating his or her doubts. *Id.*; and *Manual of Patent Examining Procedure*, § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*, at 1513.

Here, the reasoning given in support of the lack of enablement rejection is that (1) legal cases from 1959 and 1969, respectively, suggest that treatment of cancer across tissue types is unpredictable, and (2) the working examples in the specification involve only paclitaxel-resistant tumors. As to the first point, applicant submits that 30 and 40-year old legal cases have no applicability in the present case involving novel oncology compounds having a demonstrated broad spectrum of activity against various cell lines. *See* specification at page 53. The examples in this case demonstrate that the compounds of formula I and the claimed combination have activity against many cell lines, including colon, breast, ovarian, and lung cancer tissue (see specification at pages 53 through 69). The

compounds' mechanism of action as microtubule-stablizing agents provides a scientific basis to conclude they are effective against various tissue types.

As to the second point, the data in the specification is not limited to paclitaxel resistant tumors. While it is true the compounds of formula I demonstrate a broad spectrum of activity against paclitaxel sensitive and paclitaxel resistant tumors, various tumor types were tested and are described in the specification herein. Applicant respectfully invites the Examiner's attention to pages 50, 53, and 57 through 59 of the specification and the various tumor types discussed therein. Pat-7 is described as a TAXOL® resistant tumor type, but also, the discussion that follows indicates this cell line had a demonstrated multi-drug resistance in view of prior treatments with other chemotherapeutic agents (page 57, lines 10-13). HCT116/VM46 is specifically described at page 58 as a ***multi-drug resistant*** (MDR) colon carcinoma. A second multi-drug resistant tumor type is described at page 53. Thus, the specification provides support for treating other than paclitaxel-resistant tumors.

It is worth noting that enablement is not a blueprint requirement and does not require disclosure of everything needed to practice the invention. *35 U.S.C. § 112 First Paragraph Enablement Training Manual*, August 1996 (available at http:/www.uspto.gov.) Rather, "what is well-known is best omitted." *Id.* (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Enablement must be considered in view of the knowledge of the skilled artisan. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Here, there are numerous resources available to the skilled artisan in the field of oncology that provide information about different types of cancers and treatment regimens. One skilled in the art would be able to use the claimed combination of agents for treating different types of cancers.

Accordingly, for the foregoing reasons it is respectfully requested that the Section 112, first paragraph rejection be withdrawn.

B. **Section 112, Second Paragraph- Indefiniteness**

Claim 1 stands rejected as indefinite for reciting the range of proliferative diseases and then the narrower range limitation of cancer. As discussed above, claim 1 has been amended to refer to treatment of cancer. Thus, this rejection has been fully addressed.

Claim 2 is rejected for lack of antecedent basis regarding the recitation of the Formula I compound. The Examiner has requested consistency in the claims with regard to terminology and capitalization used to refer to compounds of Formula I. Claims 3-4,30-31, 9-11, 12-16, 20, 21, 22, 23, 27, and 71-72 stand rejected for analogous reasons. Applicant thanks the Examiner for making this observation and has amended the claims to provide greater consistency in the claim terminology, as discussed above.

It is believed that all Section 112, second paragraph, rejections have been addressed by the claim amendments herein.

C. Section 103, Obviousness

Claims 1-35 and 71-75 stand rejected under 35 USC § 103(a) as being obvious over Vite et al., WO 99/02514 in view of Saeki *et al.*, Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine (hereinafter "Saeki"). Vite et al., WO 99/02514 corresponds to US Pat. No. 6,605,599, which issued on August 12, 2003 and is assigned to the present assignee.

Applicant acknowledges that the compounds of the '599 patent (WO 99/02514) teach the specific compound elected by applicant herein, *i.e.,* [1S 1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17oxabicyclo[14.1.0]-heptadecane-5,9-dione. Applicant further acknowledges that WO 99/02514 generally states that the compounds claimed therein might be used in combination with a second drug that acts in a different phase of the cell cycle than the claimed compounds, as pointed out in the Office Action. However, applicant submits that Vite is not properly combined with Saeki, and further, the combination, if appropriate, would not render obvious the claimed combination of a synergistically effective amount of a compound of formula I and a cytotoxic agent as claimed herein, more particularly wherein the cytotoxic agent is an anti-metabolite, more particularly where the anti-metabolite is capecitabine.

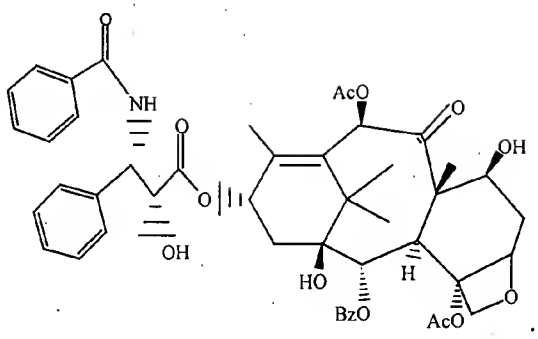
A *prima facie* case of obviousness requires that three requirements must be satisfied: (1) the prior art relied upon must contain some suggestion or motivation for modifying or combining the references; (2) the proposed modifications must have had a reasonable expectation of success; and (3) the references must teach or suggest *all* claim

limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The initial burden of satisfying these requirements rests squarely with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142.

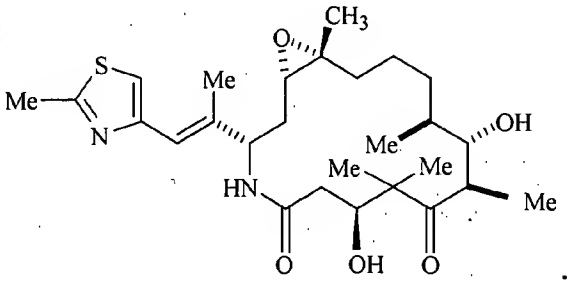
Regarding the first two elements of this test, both the motivation to combine the references and the expectation of success must be found in the prior art, not based on applicant's disclosure. *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art"). Considering the well-known phrase that "hindsight is 20-20 vision," the urge to apply hindsight with the benefit of applicant's claimed invention must be resisted, as it is improper to use hindsight to pick and choose elements to reconstruct an invention. *Smithkline Diagnostic Inc. v. Helena Labs Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468 (Fed. Cir. 1988) (one may not "pick and choose ... elements of assorted prior art references to recreate the claimed invention").

Here, the Office Action does not point to any teaching, suggestion or motivation in the prior art that would lead a skilled artisan to combine Saeki with Vite to be in possession of applicant's claimed invention, or which would establish a reasonable expectation of success with such a combination. Saeki states that an "in vivo study showed synergistic or additive effects of Capecitabine combined with anti-cancer agents (Taxanes, Mitomycin C, or Cyclophosphamide), cytokines, growth factors, and hormonal agents." This is a general statement of synergistic *or* additive effects with a range of various therapeutic agents including cytostatic, cytotoxic and hormonal agents. There is no suggestion or motivation for combining Saeki with Vite which does not claim Taxanes, Mitomycin C, Cyclophosphomaide, cytokines, growth factors, or hormonal agents, and there is no basis to conclude Saeki creates a reasonable expectation of a successful synergistic combination with a combination of compounds of formula I with capectiabine.

Notably, Paclitaxel and compounds of formula I are dissimilar in structure. Paclitaxel has the following formula (wherein Ac = acetyl),



In comparison, applicant's elected compound of formula I herein has the formula:



Additionally, compounds of formula I herein are effective in paclitaxel-resistant and paclitaxel-sensitive tumors (spec. at p. 21), demonstrating the compounds not only have different structures but different activity profiles as well. Thus, there is no basis for an obviousness argument to the effect that there is a reasonable expectation of similar properties based on similarity in structures. *Cf.* MPEP § 2144.09. As noted in the Office Action at page 4, there is a high level of unpredictability in this field.

Accordingly, for the foregoing reasons it is respectfully requested that the Section 103(a) rejection be withdrawn.

FEES

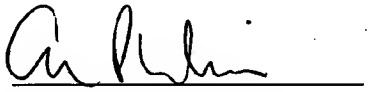
Applicant has added twenty-five new claims including one additional independent claim. However, applicant has canceled a total of thirty-six claims, and the case contains

three independent claims. Thus, is it believed no fee is due. However, in the event it is determined a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb.

SUMMARY

It is believed that all rejections of the claims have been fully addressed and that the instant claims are in condition for allowance. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

Respectfully submitted,



Anastasia P. Winslow
Attorney for Applicant
Reg. No. 40,875

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-6996

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